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New Phenoxy Benzoyl Methane Derivatives: Synthesis and Evaluation of the Antimicrobial Potential

Mohit[1*], Surendra Kumar[2], Sushil Kumar[1] and S. Riaz Hashim[1]

[1] Faculty of Pharmacy, IFTM University, Moradabad-244001 (U.P) India

[2] Gachon Institute of Pharmaceutical Science & Department of Pharmacy, College of Pharmacy, Gachon University, Incheon, Republic of Korea, 21936

ABSTRACT

In the context of the dangerous phenomenon of antimicrobial resistance to the available drugs, we present here the chemical synthesis and evaluation of a new phenoxy benzoyl methane Schiff bases (SA1-SA16), as antifungal agents. Among the compounds, SA3 was found to be most potent against *Candida albicans* when compared with the reference drugs Clotrimazole and Terbinafine. Molecular properties of the newly synthesized Schiff bases were performed by online software, and results showed good drug-like properties. The results showed new Schiff bases further optimized as a lead compound as anti-*Candida* potential.

Keywords: Schiff base, Antimicrobial activity, Molecular Properties, *Candida albicans.*

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***Address for Correspondence:**

Mohit, Faculty of Pharmacy, IFTM University, Moradabad-244001 (U.P) India.

1. INTRODUCTION

Schiff bases are the key intermediates also as common ligands in the organic synthesis and have been shown to exhibit a broad range of biological activities, including antimicrobial, antiviral, antihelmintic, antiproliferative, and antioxidant[1-8]. The imine group present in such compounds has been shown to be essential for their biological activities. Clotrimazole and Terbinafine are the antifungal drugs containing nitrogen hetero atom into their structures. The ample evidence reported in the literature on the biological potential of Schiff bases containing C=N in their structure[9-10] led us to the synthesis, physico-chemical characterization and antifungal evaluation of new Schiff bases containing nitrogen hetro atom. The pharmacokinetic and pharmacodynamic behavior of molecules inside the human body is influenced by their molecular properties, molecular size, flexibility and the presence of different pharmacophore features. The in vivo experimental determination of pharmacokinetic parameters of newly synthesized compounds is uneconomical and time consuming. From this point of view, molecular properties can predict by the online software[11]. The molecular properties of the new compounds could help to eliminate the molecules likely to fail in the early stage of drug discovery. In view of these observations, we herein report the synthesis of new Schiff bases and evaluation as antifungal agents.

2. MATERIAL AND METHODS

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. The IR spectra of synthesized compounds were recorded in potassium bromide discs on Schimadzu FTIR Spectrophotometer 8300. The 1H-NMR spectra of the synthesized compounds were recorded in $CDCl_3$ as solvent using AV-300 BROKE JEOL Spectrophotometer and tetramethylsilane (TMS) as an internal standard. All reagents were of commercial quality and were used without further purification. The reactions progress was monitored by thin-layer chromatography (TLC) using silica gel G and spots were visualized with iodine.

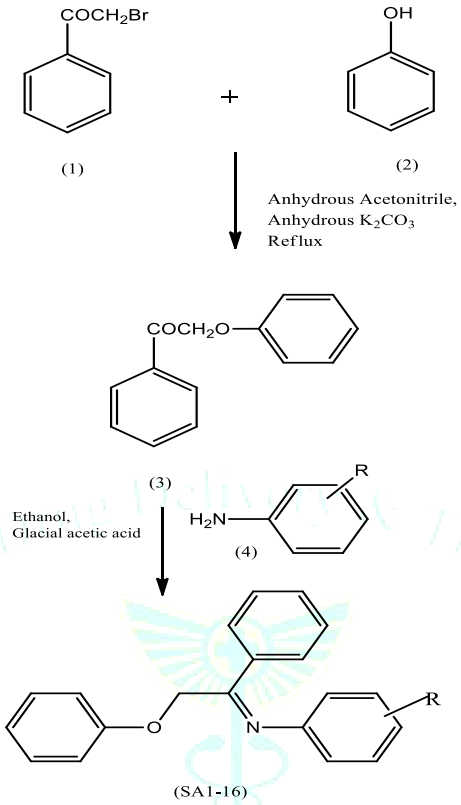
Experimental

Synthesis of 2-phenoxy-1-phenylethanone (3)

Equimolar amounts of 2-bromo-1-phenylethanone **1** (0.01mol), phenol **2** (0.01 mol) and K_2CO_3 (0.02 mol) in dry acetonitrile was refluxed for about 6 h. The mixture was filtered and solvent was removed under reduced pressure. The resulting solid was washed with excess of water. The crude product was purified by recrystallization from ethanol to afford compound **3**. Yield: 75.0 %, mp: 62-64^{o}C, R_f: 0.69 (n-Hexane: Ethyl acetate; 3:1).

General procedure for the synthesis of Schiff bases: N-(2-phenoxy-1-phenylethylidene) substituted aniline (SA1--SA16)

A mixture of compound **3** (0.01 mol), substituted aniline **4** (0.01mol) and 1 ml of glacial acetic acid in ethanol was refluxed on water bath for 8 h. The mixture was allowed to cool, and then the separated solid was filtered and recrystallized from ethanol to afford the **SA1-16**.



Scheme 1: Synthesis of Schiff bases (SA1-16).

Molecular property prediction of Schiff bases (SA1-16).

A set of molecular properties molar refractivity, topological surface area and log P were computed for the target compounds as well as two standard drugs Clotrimazole and Terbinafine using Chem 3D Ultra version 12.0, software programs. The observations are depicted in Tables1.

Table 1: Molecular property prediction of the Schiff bases (SA1-SA16).

Cpd. Code.	R	MW[a]	MR[b]	tPSA[c]	Log P
SA1	-H	287.36	89.95	21.59	4.95
SA2	4-CH_3	301.38	95.48	21.59	5.43
SA3	4-Cl	321.80	94.19	21.59	5.51
SA4	4-Br	366.25	97.28	21.59	5.78
SA5	3,4-Cl	356.25	98.80	21.59	6.06
SA6	2-NO_2	332.35	NC	73.40	4.34
SA7	3-Cl	321.80	94.19	21.59	5.51
SA8	4-NO_2	332.35	NC	73.40	4.34
SA9	4-OCH_3	317.38	96.84	30.82	4.82
SA10	2-Cl	321.80	94.19	21.59	5.51
SA11	2-Cl, 4-NO_2	366.80	NC	73.40	4.96
SA12	3-NO_2	332.35	NC	73.40	4.34
SA13	2-Br	366.25	97.28	21.59	5.78
SA14	4-F	305.35	89.99	21.59	5.11
SA15	2-OCH_3	317.38	96.84	30.82	4.82
SA16	2-CH_3	301.38	95.48	21.59	5.43
Clotrimazole		344.82	102.07	15.6	5.19
Terbinafine		291.43	99.36	3.24	5.52

Abbreviations: [a] Molecular weight, [b]Molar refractivity, [c]Topological polar surface area; NC: Not calculated.

Antimicrobial Activity

The antifungal testing was performed using the cup diffusion technique. The synthesized compounds, as 1 mg/ml solutions in dimethylformamide (DMF), were evaluated *in vitro* for activity against *C. albicans* by the cup diffusion technique[12]. Compounds showing inhibitory zones of at least 20 mm were considered active and were further evaluated for their minimal inhibitory concentration (MIC) using the two-fold serial dilution method[13]. Clotrimazole and Terbinafine were used as standard antifungal agents. Dimethylformamide was used as a control. Sterile nutrient agar was inoculated with the test organisms (each 100 mL of the medium received 1 mL of 24 h broth culture), and then seeded agar was poured into sterile petri dishes. Cups (8 mm in diameter) were cut in the agar, and each cup received 0.1 mL of the test compound solution. The plates were then incubated at 37°C for 24 h. The activities were estimated as zones of inhibition in mm diameter (Table 2). Clotrimazole and Terbinafine solutions (0.01%) were used as reference standards. DMF did not show any inhibition zones.

Minimum inhibitory concentration (MIC) measurement

Using the two-fold serial dilution method, the test organisms were grown in suitable broth for 48 h for fungi at 37°C. Two-fold serial dilutions of the test compounds solutions were prepared using the suitable broth to obtain concentrations between 1000 and 15.62 µg/mL. The tubes were then inoculated with the test organism (each 5 mL received 0.1 mL of the above inoculum) and were incubated at 37°C for 48 hr. The tubes were then observed for the presence or absence of microbial growth. The lowest concentration showing no growth was taken as the minimum inhibitory concentration. The MIC values of the prepared compounds are listed in Table 2.

3. RESULTS AND DISCUSSION

The target compounds **SA1-16** were prepared as outlined in Scheme **1**.The 2-bromo-1-phenylethanone **1** (0.01mol), phenol **2** (0.01 mol) and K_2CO_3 (0.02 mol) in dry acetonitrile was refluxed for about 6 h. The mixture was filtered and solvent was removed under reduced pressure. The obtained product was purified by recrystallization from ethanol to afford compound **3**. The Schiff bases **SA1-16** were prepared by refluxed of compound **3** with different aromatic anilines **4** in ethanol. The purity of the compounds was monitored by TLC and the structure of the compounds was deduced on the basis of spectral data. The molecular property prediction was done for the target compounds. All Schiff base have molar refractivity under 130. The topological polar surface area (tPSA) is a measure of a molecule's hydrogen bonding capacity and its value should not exceed certain limit. Topological polar surface area (tPSA) values for the test compounds were well within these limits (21.59-73.40). The log P values of test compounds were (4.34-6.06) within the range of standard drugs which shows that these compounds have a potential to effectively cross the blood brain barrier. The synthesized compounds were tested for activity against *C. albicans.* The results of antifungal activity are shown in table 2. It is evident from the results of the Schiff bases containing halogen atom like chloro, bromo and fluro at postion-4 (SA3, SA4 and SA14) were showing most potent antifungal activity as compared to the other Schiff bases. It is highlighting the importance of presence of electron withdrawing groups in the phenyl ring. The other Schiff bases (SA1, SA7-9, SA-14 and SA15) showed the variations in the antifungal activity. The ortho substituted (SA6, SA10, SA13 and SA16 except SA15) were the inactive antifungal agents in the series of Schiff's bases. Among the compound **SA3** was showed most potent antifungal activity in the synthesized compounds.

Table 2: The Antifungal Activity of Schiff bases (SA1-16).

Compound Code	Zone of Inhibition (in mm) Against *C. Albicans*	MIC (µg/ml) Against *C. Albicans*
SA-1	20	93.72
SA-2	14	>125.96
SA-3	24	15.62
SA-4	22	15.62
SA-5	16	>125.96
SA-6	16	>125.96
SA-7	20	125.96
SA-8	20	62.48
SA-9	20	62.48
SA-10	16	>125.96
SA-11	16	>125.96
SA-12	16	>125.96
SA-13	16	>125.96
SA-14	22	31.24
SA-15	20	125.96
SA-16	18	>125.96
Clotrimazole	26	1.95
Terbinafine	26	2.60

The compounds having zone of inhibition 20 mm or greater than 20 mm is considered as active.

4. CONCLUSION

The present study describes the synthesis and evaluation of antifungal activity of a series of Schiff bases. The synthesized compounds therefore, present a new scaffold that can be used to as lead in development of novel antifungal agents.

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